REMARKS

These remarks are in response to the Office Action mailed March 15, 2002.

The title has been amended to reflect the election of claims drawn to SVPH3-17 nucleic acids, and to include an additional name for this polypeptide - ADAM23 - that is readily recognized by practitioners in the art. Support for this amendment is found in the specification at page 5, lines 11-13 and at page 64, lines 9 and 18.

The specification has been amended. The amendments do not introduce any new matter and were made to correct typographical or grammatical errors, to remove instances of "www" and "html" that might generate unintended hyperlinks, and to include the alternative names ADAM22 for SVPH3-13 and ADAM23 for SVPH3-17.

Claims 17-18, 25, and non-elected claims 19-20, 24, and 26-29 have been canceled without prejudice to Applicant's right to prosecute the canceled subject matter in any divisional, continuation, continuation-in-part, or other application.

Claims 15 and 22-23 have been amended, and new claims 30-46 have been added. Support for the amendments to the claims and for the new claims can be found in the claims and specification as originally filed. For example, support for the amendments to claim 15 can be found in the specification at page 57, lines 13-14 of Table 3. Support for the amendment to claim 22 can be found in the specification at page 27, line 3 through page 33, line 31; and at page 64, lines 9 and 18. Support for new claim 30 can be found at page 27, lines 9-10. Support for new claims 31-33 can be found *inter alia* in the specification at page 11, line 25; page 16, lines 24-25; page 17, lines 14-17; page 19, line 30 through page 20, line 6; page 22, line 24 through page 27, line 1; and at page 57, lines 13-14 of Table 3. Support for new claims 34-37 can be found, for example, in the specification at page 11, line 25; page 15, lines 1-8; page 17, lines 2-6; page 18, lines 29-30; and at page 57, lines 13-14 of Table 3. For new claims 38-46, support can be found in the specification at page 11, lines 22-26; page 54, lines 5, 9, and 11 of Table 1; at page 56, lines 29-32 of Table 3; at page 57, lines 2, 5, 7-9, 11, 13-14, and 17-20 of Table 3; and at page 64, lines 9 and 18. No new matter is believed to have been added.

Attached hereto is Appendix A, captioned "Version with Markings to Show Changes", which shows the amendments made to the title, specification, and claims using standard notation (underlining and bracketing). Appendix B presents the

pending claims in rewritten form. Applicant respectfully requests reconsideration and allowance of the claims pending.

I. RESPONSE TO RESTRICTION REQUIREMENT

Applicant affirms the election of Groups II and IV claims (claims 15-18, 21-23, and 25) drawn to "nucleic acid molecules that either comprise the nucleic acid sequence set forth in SEQ ID NO:2 or encode the same polypeptide, and nucleic acid molecules comprising portions of such nucleic acid molecules related to SEQ ID NO:2 that specify polypeptides comprising discrete domains of the encoded polypeptide of SEQ ID NO:4". Claims drawn to "the encoded polypeptide of SEQ ID NO:4 and polypeptides comprising discrete domains thereof" are presented in a divisional application of the present application, filed July 23, 2002. Claims 17-18, 25, and non-elected claims 19-20, 24, and 26-29 have been canceled. New claims 30-46 are consistent with the elected invention.

II. OBJECTIONS TO THE CLAIMS

Claim 22 is objected to because, as the Office Action notes, there was no period at the end of the claim. Applicant has amended claim 22 to include a period. Accordingly, the objection is moot and may be withdrawn.

III. REJECTION UNDER 35 U.S.C. §101 and §112, First Paragraph

Claims 15-18, 21-23, and 25 were rejected under 35 U.S.C. §101 and §112, first paragraph, on the basis that these claims allegedly lack patentable utility, and that one skilled in the art would therefore not know how to use the invention. Applicant respectfully traverses this rejection.

The Office Action makes a distinction between the utility of the SVPH3-17 (ADAM23) metalloprotease and nucleic acids encoding it, and the utility of the **disintegrin** region of ADAM23 and nucleic acids encoding this **disintegrin** region. In the indication of allowable subject matter at pages 14-15 of the Office Action, the Examiner has helpfully noted:

> While the elected claims are rejected above under 35 U.S.C. §§101 and 112, first paragraph, and claims 15, 22 and 25 are rejected under the second paragraph of 35 U.S.C. §112, the subject matters of clauses (a), (b) and (e) of claim 15 describing nucleic acid sequences comprising nucleic acid sequences identical to, or isocoding with, SEQ

> ID NO:2, as well as genera of clauses (f) and (h) which are nucleic acid sequences encoding a **disintegrin** region of SEQ ID NO:4 - a region comprising at least amino acid positions 496-599 of SEQ ID NO:4 - are free of the above rejections and are free of the prior art of record as well. [Emphasis added]

The Examiner is requested to note that claim 15 as amended, dependent claims 16 and 21-23 as amended, and new claims 30-46 all refer to polynucleotides encoding SEQ ID NO:4 or fragments or variants thereof having **disintegrin** activity. For example, claim 15 as amended retains the clauses (a), (b), (f), and (h) - which are now clauses (a) through (d) - that the Office Action indicated as containing allowable subject matter. Claims 17-18 and 25 have been canceled, rendering objections to these claims moot. For at least these reasons, withdrawal of the rejection of claims 15-18, 21-23, 25 and new claims 30-46 under 35 U.S.C. §101 is respectfully requested.

Further, Applicant submits that additional uses identified by the specification for the SVPH3-17 (ADAM23) polynucleotide are also credible, specific, and substantial. For example, the SVPH3-17 polynucleotides and polypeptides find a credible, specific, and substantial use as tissue markers. At page 47, lines 18-23, in Example 1 at page 64, and in Figures 1 and 2 of the specification, Applicant demonstrates that the SVPH3-17 nucleic acid molecules can be used to identify specific tissues. The Examiner is requested to note that in Figure 1, SVPH3-17 nucleic acid molecules react with RNA derived from heart tissue, but not with RNA from neighboring organs such as lung and liver. Therefore, SVPH3-17 nucleic acid molecules have credible, specific, and substantial uses in, for example, distinguishing heart tissue from lung or liver tissue.

Applicant submits that they have shown substantial, credible and specific utility for the claimed SVPH3-17 polynucleotides and polypeptides based on *in vitro* assays and methods well known in the art. Accordingly, for at least the above reasons, Applicant respectfully requests withdrawal of the rejection of claims 15-18, 21-23, and 25 under 35 U.S.C. §101 and §112, first paragraph.

IV. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 15-18, 21-23, and 25 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art

that the inventor, at the time the application was filed, had possession of the claimed invention. With respect to the elected invention, the Office Action indicates that claims 15(a), (b), (e) and at least one genera of (f) that comprises nucleic acid molecules encoding fragments of SEQ ID NO:4 that exhibit at least disintegrin activity, are not subject to the present rejection as Applicant is considered to have been in constructive possession of the invention described by these certain species and genera at the time the invention was made.

Claims 17-18 and 25 have been canceled without prejudice to be presented in a subsequent application, rendering moot the rejection of these claims.

With respect to claim 15 and dependent claims 16 and 21-23, claim 15 has been amended to retain clauses (a) and (b), and that portion of clause (f) - now clause (c) -that refers to nucleic acid molecules encoding fragments of SEQ ID NO:4 that have disintegrin activity. Clauses (d) and (e) of claim 15 as amended also specify nucleic acid molecules encoding fragments of SEQ ID NO:4 that have disintegrin activity, and in addition recite particular amino acid sequences or subsequences of the disintegrin domain of SEQ ID NO:4. All clauses of claim 15 as amended therefore should not be subject to the rejection of claim 15 as discussed in the Office Action and the above paragraph. For at least these reasons, withdrawal of the rejection of claims 15-18 and 21-23 is respectfully requested.

Claims 15-18, 21-23, and 25 were also rejected under 35 U.S.C. §112, first paragraph because the specification, while being enabling for preparation of nucleic acid sequences encoding fragments of SEQ ID NO:4 having disintegrin activity and such an encoded fragment of SEQ ID NO:4, allegedly does not reasonably provide enablement for preparation of nucleic acid sequence encoding a polypeptide having an amino acid sequence that diverges, by virtue of amino acid substitutions, deletions and insertions, or combinations thereof at as many as 30% of the amino acid positions from that of SEQ ID NO:4.

Claims 17-18 and 25 have been canceled without prejudice to be presented in a subsequent application, rendering moot the rejection of these claims. Claim 15 has been amended to remove clause (c) that apparently contained the subject matter related to the basis for the rejection. For at least these reasons, withdrawal of this rejection of claims 15-18, 21-23, and 25 under 35 U.S.C. §112, first paragraph is respectfully requested.

Furthermore, the concern expressed in the Office Action about the enablement of amino acid sequences having substitutions, deletions, or insertions relative to SEQ ID NO:4 and retaining biological activity was based on an assumption that the placement of these changes would be 'arbitrary' (Office Action, bottom of page 10). This assumption was misplaced, as shown by the following. In addition to description of the SVPH3-17 (ADAM23) disintegrin domain (at page 11, line 25), the specification notes that the SVPH3-17 (ADAM23) polypeptide is homologous (i.e. shares amino acid sequence similarity with) members of the ADAM family including fertilin-alpha (page 12, line 10 of the specification). At the time of filing of the priority application, those of skill in the art were aware of conserved structural features of disintegrin domains within polypeptides such as fertilin-alpha, and the relationship between these features and the functions of these domains (see Exhibit 1, Jia *et al.*, 1997, *J. Biol. Chem.* 272: 13094-13102).

Figure 1 of Exhibit 1 shows the sequence similarity between disintegrin domains such as those of murine fertilin-alpha and fertilin-beta, and snake venom disintegrin domains such as that of atrolysin A. Of particular note in Figure 1 of Exhibit 1 is the conservation of the overall number and arrangement of cysteine residues between disintegrin domains, and particularly between the eight disintegrin domain amino acid sequences in the lower part of Figure 1. The Exhibit 1 reference also presents data relating to the biological activity of disintegrin domain peptides that vary from the atrolysin A disintegrin domain sequence (see pages 13098-9 and Table I on page 13100). Exhibit 2 presents an amino acid sequence alignment showing the amino acid sequence similarity between the disintegrin domain region of ADAM23 polypeptide (amino acids 496 through 599 of SEQ ID NO:4) and the disintegrin domains of fertilin-alpha, fertilin-beta, and atrolysin A. ADAM23 polypeptide has the 15 conserved cysteine residues present in these other disintegrins. A comparison of the type shown in Exhibit 2 makes readily apparent to those of skill in the art that the spacing between cysteine residues is generally well conserved, but less so between cysteines 3 and 5 and between cysteines 6 and 7. Also, the amino acid residues between cysteines 3 and 5 and between cysteines 6 and 7 show a lesser degree of sequence conservation. One of skill in the art would naturally conclude that amino acid substitutions, insertions, or deletions in these regions, for example, would more likely result in a biologically active variant polypeptide, than changes in other regions within the disintegrin domain.

Therefore, based on information readily available to those of skill in the art as exemplified by Exhibits 1 and 2, such artisans would have substantial guidance, based on the knowledge in the art at the time, in making variants of SEQ ID NO:4 that retain disintegrin activity.

For at least the foregoing reasons, Applicant respectfully requests withdrawal of the rejection of claims 15-18, 21-23, and 25 under 35 U.S.C. §112, first paragraph.

V. REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 15, 22, and 25 stand rejected under 35 U.S.C. §112, second paragraph as allegedly failing to set forth distinctly the subject matter which applicant(s) regard as their invention. Claim 25 has been canceled without prejudice, rendering moot the rejection of this claim.

Claim 15 was rejected on the basis that "a nucleic acid molecule encoding an amino acid sequence comprising the amino acid sequence of SEQ ID NO:4" was present twice within the claim - in clauses (b) and (e). Claim 15 has been amended to remove clause (e) as previously presented, obviating the basis for the rejection.

Claim 22 was rejected on the basis that the claim was drawn to a method of *producing* an ADAM23 polypeptide, but a method step specifying recovery of the polypeptide was recited not in claim 22 but in dependent claim 23. While applicants do not accede to the basis for the rejection, claim 22 has been amended to recite a method for *expression* of a polypeptide in a host cell, and claim 23 has been amended to conform to claim 23. This amendment does not narrow the scope of claims 22 and 23.

For at least the above reasons, Applicant respectfully requests withdrawal of the rejection of claims 15, 22, and 25 under 35 U.S.C. §112, second paragraph.

Supplemental Information Disclosure Statement (IDS)

A Supplemental IDS and accompanying Form PTO-1449 are being submitted with this response.

Should the Examiner have any questions, or believes that a teleconference would be helpful to clarify or advance the present application to allowance, the Examiner is invited to call the undersigned attorney at (206) 265-4071.

The Examiner is authorized to charge any required fees or credit any overpayments to Deposit Account Number 09-0089.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C., 20231, on the date indicated below:

Date: August 15, 2002 Signed: Elizabeth M. McCarthy